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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/085,476	02/27/2002	Raffaele De Francesco	IT0002PCA	5843

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EXAMINER	
HUTSON, RICHARD G	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 10/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	10/085,476	DE FRANCESCO ET AL.	
	Examiner	Art Unit	
	Richard G. Hutson	1652	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 16 September 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: *20, 21*.
   Claim(s) objected to: _____.
   Claim(s) rejected: *12,14,17,18,22 and 23*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

RICHARD HUTSON, PH.D.
PRIMARY EXAMINER

Continuation of 11. does NOT place the application in condition for allowance because: Claims 12, 14, 17, 18, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tomei et al. (Journal of Virology 67(7): 4017-4026, July 1993).
The rejection was stated in the previous office action as it applied to previous claims 12, 14, 17 and 18 and repeated below.
Tomei et al. teach that the Hepatitis C virus (HCV) is considered to be the major etiologic agent of post-transfusion non-A, non-B hepatitis and that the NS5 region of the HCV polyprotein is cleaved into two smaller products of 47 and 65 kDa. Tomei et al. also teach that the NS5B region contains a GDD sequence characteristic of RNA-dependent RNA polymerases (RdRp) and they suggest that this protein may act as a viral RNA replicase during HCV-specific RNA synthesis and also function in the replication of the viral genome, acting as a component of the replication complex involved in the reaction (page 4024, column 1, paragraph 5). Tomei et al. further teach DNA constructs and transient expression of the HCV genome and characterize the post-translational processing of the HCV transcript, and specifically transcribe and translate NS5B, described by SEQ ID NO: 1. (see page 4020, Figure 1 and also Figure 3A).
One of ordinary skill in the art at the time of the filing of the invention would have been motivated to incubate together the HCV NS5B protein, ribonucleotide substrates and a RNA template under conditions suitable to produce RNA-dependent RNA polymerase, wherein said incubation takes place in vitro in order to further characterize the function and role of the protein(s) encoded by the NS5B ORF. The expectation of success comes from the high degree of skill in the art with respect to protein expression, as demonstrated by Tomei et al. in their expression of the HCV cDNA encoding the entire polyprotein using a vaccinia virus T7 expression system. One of ordinary skill at the time of invention would have been motivated to produce the NS5B protein both by the independent transcription and translation of the NS5B as well as by the proteolytic processing of the NS2-NS3-NS4-NS5 polyprotein to determine if the proteolytic processing event affects the activity of the NS5B protein product. One would have been further motivated to vary the RNA templates and primers in the incubation mixture to characterize the specific mechanism of action of any RNA-dependent RNA polymerase activity. The motivation for the addition of ribonucleotide substrates and a RNA template comes from the suggestion by Tomei et al. that the NS5B encodes a RNA-dependent RNA polymerase. The reasonable expectation of success comes from the teaching of Tomei et al. that while the nonstructural region of the HCV genome has not been characterized in detail, it is thought to be processed in a manner similar to that of flaviviruses and pestiviruses and the hydropathy profile of HCV polyprotein is similar to that of the flavivirus polyprotein as well as the suggestion that the NS5B ORF encoded protein is a RNA-dependent RNA polymerase. One of ordinary skill in the art at the time of filing of the application would have been further motivated to incubate together the HCV NS5B protein, ribonucleotide substrates and a RNA template under conditions suitable to produce RNA-dependent RNA polymerase activity, wherein said incubation takes place in vitro in the presence of potential target molecules which may inhibit the action of the NS5B protein as a means of identifying potential therapeutics to be used against the NS5B protein and HCV. The motivation for why one of skill in the art would be interested in the function of the NS5B ORF is because as one of only a few HCV encoded nonstructural proteins the protein(s) encoded by the NS5B ORF is a prime target for the development of therapeutics against HCV. A reasonable expectation of success comes from the high degree of knowledge in the art with respect to protein expression and the identification of inhibitors of said proteins activity, as discussed above.

In response to the previous rejection, applicants have amended claim 20 and 23 and traverse the rejection as it applies to the newly amended claims.

Applicants continue to traverse the rejection on the basis that the prior art uncertainty as to whether NS5B is an authentic HCV protein, taken together do not provide: (1) a motivation to modify Tomei et al. to obtain the claimed assay; or (2) a reasonable expectation of success in modifying Tomei et al. to obtain the claimed assay.

Applicants continue to argue that prior art was uncertain concerning the relevance of recombinantly produced NS5B to authentic HCV proteins and repeat such supporting citations.

Applicants continue to submit the apparent failure and difficulty encountered by others in successfully purifying HCV RNA-dependent RNA polymerase and a long-felt need for an HCV RNA-dependent RNA polymerase assay further illustrate the inventive nature of the pending claims.

Applicants' complete argument is acknowledged, however, continues to be found non-persuasive for the reasons previously stated on the record and those below. With respect to applicants point, that the prior art is uncertain if NS5B corresponds to an authentically produced HCV protein; as this would effect (1) motivation and (2) expectation of success, applicants' are reminded, as previously stated, Tomei et al. teach that the NS5 region of the HCV polyprotein is cleaved into two smaller products of 47 and 65 kDa and the NS5B region contains a GDD sequence characteristic of RNA-dependent RNA polymerases (RdRp) and they suggest that this protein may act as a viral RNA replicase during HCV-specific RNA synthesis and also function in the replication of the viral genome. Applicants have produced no evidence to the contrary.

Finally with respect to applicants comments regarding the apparent failure and difficulty encountered by others as well as a long-felt need, applicants comments are acknowledged, however, not found persuasive for the reasons previously made of record. Applicants are reminded that this is a rejection based on the obviousness of the claimed methods and that applicants should argue such that applicants arguments are clearly directed to the rejection of record, as it applies to the claimed methods.

Thus claims 12, 14, 17 and 18 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Tomei et al.